REMARKS

In the Office Action dated August 31, 2001, claims 23-621 were rejected. In response to the Office Action claims 23, 26-35, 38-40, 42, 43, 52, 53, 65-76, 81-86, 91-95, 111-113, 122, 123, 130, 131, 141, 144, 170, 171, 181, 184, 198, 203, 219, 229, 230, and 233 are amended; claims 24, 25, 36, 37, 41, 44-51, 54-64, 77-80, 87-90, 124-126, 142, 143, 164-166, 182, 183, 223-225, 238-621 are canceled; and claims 622-861 are added. Applicant respectfully submits that no new matter has been added by way of this amendment. Upon entry of this Amendment, claims 23, 26-35, 38-40, 42, 43, 52, 53, 65-76, 81-86, 91-123, 127-141, 144-163, 167-181, 184-222, 226-237, and 622-861 are pending and under consideration in the present application.

Applicant thanks the Examiner for the interview of July 16, 2001. As requested during the interview, Applicant has canceled claim 56 and rewritten it as new independent claim 622. New claims 623-654 depend from claim 622. New method claims 655-661 recite the dosage form of claim 622, and new liquid pharmaceutical claims 662-665 also recite the dosage form of claim 622.

Also submitted herein, on a separate page titled "Version with Marking to Show Changes Made to the Claims," is a marked-up copy of prior pending claims 23, 26-35, 38-40, 42, 43, 52, 53, 65-76, 81-86, 91-95, 111-113, 122, 123, 130, 131, 141, 144, 170, 171, 181, 184, 198, 203, 219, 229, 230, and 233. This page shows the changes made to prior pending claims 23, 26-35, 38-40, 42, 43, 52, 53, 65-76, 81-86, 91-95, 111-113, 122, 123, 130, 131, 141, 144, 170, 171, 181, 184, 198, 203, 219, 229, 230, and 233, and how these claims, as amended, now stand before the Patent Office.

Applicant is also providing the Examiner with an English translations of Japanese Patent Applications No. 05194225.

As established below, Applicant submits that the pending claims are patentable over the prior art.

I. Obviousness-type Double Patenting Rejection

Claim 95 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 5,840,737. A terminal disclaimer is enclosed in response to this rejection. Withdrawal of this rejection is respectfully requested.

II. Rejections Under 35 U.S.C. §102(b)

The Examiner rejected claims 23-33, 95-111, 141-151, 300-311, 335-370, 461-491, and 496-531 under 35 U.S.C. § 102(b) as being anticipated by JP05194224 or JP05194225 by Oishi *et al.* The Examiner stated that the claim language as presented reads on the reference since "comprising" is an open-ended term. Claims 300-311, 335-370, and 461-491 have been canceled. Independent claims 23, 95, and 141, have been amended to better define the invention and are not anticipated by Oishi *et al.* This rejection is respectfully traversed.

The disclosures of Oishi *et al.*, Japanese Patent Application Nos. 05194224 (Oishi '224), and 05194225 (Oishi '225) do not anticipate the pending claims. For a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art. *See In re Spada*, 911 F.2d 705, 708, 15 USPQ 2d 1655, 1657 (Fed. Cir. 1990) ("[T]he [prior art] reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it." (citations omitted)). Motorola, Inc. v. Interdigital Technology

Corp., 43 USPQ 2d 1481, 1490 (Fed. Cir. 1997). In addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public. *Akzo N.V. v. United States International Trade Commission*, 1 USPQ 2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987)

The emphasis of the cited references is on using buffering agents in an intermediate core part to prevent degradation of the proton pump inhibitor by the enteric coating—not gastric acid. Furthermore, Oishi '225 and '224 do not enable one of ordinary skill to practice the present claimed invention. As stated by the Federal Circuit: "[O]ur precedent states that a reference must be enabling to be prior art, that precedent simply means that a reference...is prior art only for that which the reference enables." The F.B. Leopold Company, Inc. v. Roberts Filter Manufacturing Company, Inc., Civ App. 96-1218, slop op. at 5-6 (Fed. Cir. July 2, 1997) (unpublished). Thus, an anticipatory reference must be enabling, that is, it must put the claimed invention in the hand of one skilled in the art. Both Oishi '225 and '224 fail this test.

(i) Claims 23-33

As the claims now stand in front of the Patent Office, claim 23 claims a solid composition in a dosage form that is **not enteric-coated**, consisting essentially of a proton pump inhibitor, and at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. The dosage form is in the form of a suspension tablet, a chewable tablet, an effervescent powder, and an effervescent tablet. Claims 26-35, 38-40, 42, 43, 52, 53, 65-70, 81-86, 91-94 depend from claim 23.

The Oishi *et al.* patents, Japanese Patent Application Nos. 05194224 and 05194225, focus on preparing enteric coated dosage forms and intermediate core parts thereof. Specifically, Oishi '225 teaches a "preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, with a benzimidazole compound that has antiulcer action and is not stable in acids." Oishi '225, at claim 1. Oishi '225 states that this preparation can be a "tablet, granule or capsule" Oishi '225, at claim 5; [0004]. However, when read in context of the entire specification, such tablets, granules and capsules refer to intermediate forms that are then enteric coated for the finished dosage forms. This is emphasized by Oishi '225's description of the prior art and problems to be solved by the invention:

> With preparations such as tablets, fine powders, granules, capsules and dispersions, the compounds are influenced by other components of the preparation formula and become unstable, leading to a decrease in content and discoloration over time. Among these preparations, **when the compounds are coated to produce granules, they have poor compounding properties with respect to enteric bases** (cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, and methacrylic acid acrylic acid copolymer), and suffer content decrease and discoloration. **When an oral preparation is to be manufactured** in this manner using benzimidazole compound, in addition to problems arising from the **need for compounding with other components and the use of enteric base coatings**, there are also difficulties with formulation due to the detrimental influences on stability as described above. Consequently, it is **necessary** to appropriately stabilize these compounds when they are to be formulated in oral dosage forms.

Oishi '225, at [0001] (emphasis added).

Section [0004] on page 5 describes how the intermediate core compositions are obtained by uniformly blending the benzimidazole compound, the amino acid, amino acid acid salt or

amino acid alkali salt stabilizer, the buffering agent, additives, and water. Amounts of these substances disclosed are in the ranges of 0.01-10 parts by weight of amino acid and 0.01-10 parts by weight of buffer with respect to 1 part by weight of benzimidazole compound.

However, none of the embodiments in Oishi '225 describe or teach the present claimed invention where the composition has at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. As illustrated below in Table No. 1, the amount of buffering agent in the embodiments of Oishi '225 is **never greater than 2.5 mg**:

Table No. 1. Oishi '225 Working Examples

Example No.	Omeprazole (mg)	Buffering Agent (mg)	Ratio of Omeprazole to Buffering Agent (weight to weight)
1	5.0	2.5	1:0.5
2	5.0	1.0	1:0.2
3	5.0	1.5	1:0.3
4	5.0	1.5	1:0.3
5	20.0	3	1:0.15
6	20.0	3	1:0.15
7	5.0	2.0	1:0.4

Oishi '225 states further that the "resulting mixture is then finely granulated with a wet granulator, and the material is then subjected to tabletization to produce uncoated tablets for

tablet production. Alternatively, the material can be granulated using an extrusion granulator, and then formed into core granules for producing granules." Oishi '225, at [0004] (emphasis added). The application then states that "[t]he uncoated or core granules **obtained in this manner** can be formed into an enteric preparation by coating the core granules with enteric coating," and that:

> The **enteric tablet or granule** that is of a dosage form that is **appropriate for oral administration** can be obtained as described above, and in addition, the granules can be packaged into capsules to produce a capsule. The **preparation obtained in this manner** experiences little change in external appearance even over long-term storage, and exhibits excellent stability with almost no decrease in content. As a result, the preparations can be used in the treatment of digestive ulcers in mammals including humans.

Oishi '225 at [0005].

Oishi '224 teaches when benzimidazole compounds that are unstable in acid are compounded with a combination of aluminum glycinate and buffering agent, the benzimidazole compounds is markedly stabilized, and coloration does not take place. Oishi '224, at abstract. Oishi '224 further teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added). The problem solved by Oishi '224 is that it is necessary to stabilize the compounds before making compounds into preparations for oral administration. Oishi '224 discovered that the preparations can be stabilized during the preparation of oral dosage forms through the use of aluminum glycinate and buffering agent. Oishi '224 at [0002]. Amounts of the buffering agent disclosed range from 0.01-20 parts by weight with respect to 1 part by weight of the benzimidazole compound. Oishi '224 at [0003].

However, none of the embodiments in Oishi '224 describe or teach the present claimed invention where the composition has at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as

to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. As illustrated in Table No. 2, below, the amount of buffering agent in the embodiments of Oishi '224 is **never greater than 2.0 mg**:

Table No. 2. Oishi '224 Working Examples

Example ID. No.	Omeprazole (mg)	Buffering Agent (mg)	Ratio of Omeprazole to Buffering Agent (weight to weight)
Embodiment 1	5.0	2.0	1:0.4
Embodiment 2	5.0	1.5	1:0.3
Embodiment 3	5.0	1.5	1:0.3
Embodiment 4	20.0	1.0	1:0.05
Embodiment 5	20.0	1.0	1:0.05
Embodiment 6	5.0	2.0	1:0.4
Reference 1	20.0	1.0	1:0.05
Reference 2	20.0	1.0	1:0.05

Therefore, Oishi '225 and '224 do not describe or teach the present claimed invention where the dosage form is not enteric coated and that has at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor. Additionally, the Oishi *et al.* patents do not teach or describe the presently claimed dosage forms of a suspension tablet, a chewable tablet, an effervescent powder, or an effervescent tablet.

Reconsideration and withdrawal of this rejection is respectfully requested.

(ii) Claims 95-111

As the claims now stand in front of the Patent Office, claim 95 claims a method of treating an acid-related gastrointestinal disorder by enterally administering to a subject a solid pharmaceutical composition in a dosage form that is **not enteric-coated.** The composition consists essentially of a proton pump inhibitor, and at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in the subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. Claim 96-111 depend from claim 95.

Because there is no teaching in the Oishi *et al.* patents as to the oral administration of the intermediate cores, Applicant's method claims are not anticipated. As mentioned above, the Oishi *et al.* patents, Japanese Patent Application Nos. 05194224 and 05194225, focus on preparing enteric coated dosage forms and intermediate core parts thereof. These enteric coated dosage forms are administration to a subject. Claims 95-111 claim a method of enterally administering a solid pharmaceutical composition in a dosage form that is **not enteric-coated.**

As mentioned above, Oishi '225 teaches a "preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, with a benzimidazole compound that has antiulcer action and is not stable in acids." Oishi '225, at claim 1. Oishi '225 states that this preparation can be a "tablet, granule or capsule" Oishi '225, at claim 5; [0004]. However, when read in context of the entire specification, such tablets, granules and capsules refer to intermediate forms that are then enteric coated for the finished dosage forms.

Similarly, Oishi '224 teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added).

Reconsideration and withdrawal of this rejection is respectfully requested.

(iii) Claims 141-151

As the claims now stand in front of the Patent Office, claim 141 claims a composition, consisting essentially of a proton pump inhibitor; gastric secretions; and at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by the gastric secretions so as to achieve bioavailability of the proton pump inhibitor in a subject. The proton pump inhibitor and the buffering agent comprise a solid dosage form, which is capable of disintegration and dissolution in the gastric secretions and is **not enteric-coated**. Claims 142-151 are dependent from claim 141.

The Oishi *et al.* patents, Japanese Patent Application Nos. 05194224 and 05194225, focus on preparing enteric coated dosage forms and intermediate core parts thereof. These references do not teach the present claimed composition of claims 141-151 that contain at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by the gastric secretions so as to achieve bioavailability of the proton pump inhibitor in a subject, and where the proton pump inhibitor and the buffering are in a solid dosage form that is capable of disintegration and dissolution in the gastric secretions and is **not enteric-coated**.

Neither of these cited references teach the oral administration of the uncoated intermediate cores, nor do the cores meet the limitations of the Claims. Consequently, there is

no teaching that such intermediate cores interact with gastric secretions to form the composition as claimed by Applicant. Indeed, the prior art teaches that such cores must have enteric coatings. There is thus no teaching in Oishi '225 or in Oishi '224 that the intermediate tablets and granules are suitable for oral administration. Indeed, it is only the enteric "preparation obtained in this manner" from these references that is appropriate for oral administration and can be used to treat digestive ulcers.

Reconsideration and withdrawal of this rejection is respectfully requested.

(iv) New Claims 622-654

As the claims now stand in front of the Patent Office, claim 622 claims a solid pharmaceutical composition in a dosage form that is **not enteric-coated**. The composition contains a **non-enteric coated** proton pump inhibitor, and a mixture of sodium bicarbonate and a calcium salt. The mixture of sodium bicarbonate and calcium salt is in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. Claims 623-645 depend from claim 622.

As mentioned above, the Oishi *et al.* patents, Japanese Patent Application Nos. 05194224 and 05194225, focus on preparing enteric coated dosage forms and intermediate core parts thereof. These references do not teach the present claimed composition of claims 622-645 that is in a dosage form that is **not enteric coated**, and contains a mixture of sodium bicarbonate and calcium salt in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form.

Specifically, Oishi '225 does not describe or teach the present claimed invention where the composition has a mixture of sodium bicarbonate and a calcium salt in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. As illustrated above in Table No. 1, the amount of buffering agent in the embodiments of Oishi '225 is **never greater than 2.5 mg.**

Similarly, Oishi '224 teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added). As illustrated above in Table No. 2, the amount of buffering agent in the embodiments of Oishi '224 is **never greater than 2.0 mg.**

Therefore, the disclosures of the Oishi *et al.* patents do not anticipate pending claims 622-654.

(v) New Claims 666-717

As the claims now stand in front of the Patent Office, claim 666 claims a solid pharmaceutical composition in a dosage form that is not enteric-coated. The composition consists essentially of a non-enteric coated proton pump inhibitor, and a buffering agent in an amount more than about 20 times the amount of the proton pump inhibitor on a weight to weight basis in the composition. Claims 667-717 depend from claim 666.

The Oishi *et al.* patents focus on preparing enteric coated dosage forms and intermediate core parts thereof. These patents do not teach or describe a composition with an amount of a buffering agent that is more than 20 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

Therefore, the disclosures of the Oishi *et al.* patents do not anticipate pending claims 666-617.

(vi) Method Claims: 203-222, 226-237; and New Method Claims: 655-661, 718-724, 725-728, 747-752, and 785-791

As the claims now stands in front of the Patent Office, Claims 203 a method of treating an acid-related gastrointestinal condition in a subject in need thereof, by enterally administering to the subject the solid pharmaceutical dosage form as recited in Claim 181. Claims 204-222, 226-237 are depend from claim 203. Claim 655 claims a method for treating an acid-related gastrointestinal disorder in a subject in need thereof, comprising: enterally administering to the subject the solid pharmaceutical composition as recited in Claim 622. Claims 656-661 are depend from claim 655. Claim 718 claims a method for treating an acid-related gastrointestinal disorder in a subject in need thereof, comprising: enterally administering to the subject the solid pharmaceutical composition as recited in Claim 666. Claims 719-724 are depend from claim 718. Claim 725 claims a method for administering a liquid pharmaceutical composition to a subject, by combining the pharmaceutical composition as recited in Claim 666 with an aqueous medium to form a suspension, and orally administering the suspension to the subject in a single dose without administering an additional buffering agent. Claims 726-728 are depend from claim 725. Claim 747 claims a method for treating an acid-related gastrointestinal disorder in a subject in need thereof, comprising: enterally administering to the subject the solid pharmaceutical composition as recited in Claim 23. Claims 748-752 depend from claim 841. Claim 785 claims a method for treating an acid-related gastrointestinal disorder in a subject in

need thereof, comprising: enterally administering to the subject the solid pharmaceutical composition as recited in Claim 141. Claims 786-791 depend from claim 785.

Because there is no teaching in the Oishi *et al.* patents as to the oral administration of the intermediate cores, Applicant's method claims are not anticipated. As mentioned above, the Oishi *et al.* patents focus on preparing enteric coated dosage forms and intermediate core parts thereof. These enteric coated dosage forms are administration to a subject.

Specifically, Oishi '225 teaches a "preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, with a benzimidazole compound that has antiulcer action and is not stable in acids." Oishi '225, at claim 1. Oishi '225 states that this preparation can be a "tablet, granule or capsule" Oishi '225, at claim 5; [0004]. However, when read in context of the entire specification, such tablets, granules and capsules refer to intermediate forms that are then enteric coated for the finished dosage forms. This is emphasized by Oishi '225's description of the prior art and problems to be solved by the invention:

> With preparations such as tablets, fine powders, granules, capsules and dispersions, the compounds are influenced by other components of the preparation formula and become unstable, leading to a decrease in content and discoloration over time. Among these preparations, **when the compounds are coated to produce granules, they have poor compounding properties with respect to enteric bases** (cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, and methacrylic acid acrylic acid copolymer), and suffer content decrease and discoloration. **When an oral preparation is to be manufactured** in this manner using benzimidazole compound, in addition to problems arising from the **need for compounding with other components and the use of enteric base coatings**, there are also difficulties with formulation due to the detrimental influences on stability as described above. Consequently, it is **necessary** to

> appropriately stabilize these compounds when they are to be formulated in oral dosage forms.

Oishi '225, at [0001] (emphasis added).

Similarly, Oishi '224 teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added).

Therefore, the disclosures of the Oishi et al. patents do not anticipate pending claims 203-222, 226-237, 655-661, 718-724, 725-728, 747-752, and 785-791.

Reconsideration and withdrawal of this rejection is respectfully requested for claims 203-222, and 226-237..

(vii) New Liquid Claims: 662-665, 753-756, 792-795, 827-831

As the claims now stand in front of the Patent Office, claim 662 claims a liquid pharmaceutical composition, comprising: the dosage form as recited in Claim 622 suspended in an aqueous medium. Claims 663-665 depend from claim 662. Claim 753 claims a liquid pharmaceutical composition, comprising: the pharmaceutical composition as recited in Claim 23 and an aqueous medium. Claims 754-756 depend from claim 753. Claim 792 claims a liquid pharmaceutical composition, comprising: the pharmaceutical composition as recited in Claim 141 and an aqueous medium. Claims 793-795 depend from claim 792. Claim 827 claims a liquid pharmaceutical composition, comprising: the pharmaceutical composition as recited in Claim 181 and an aqueous medium. Claims 828-831 depend from claim 827.

Because there is no teaching in the Oishi *et al.* patents as to liquid pharmaceutical compositions, Applicant's method claims are not anticipated. As mentioned above, the Oishi *et*

al. patents focus on preparing enteric coated dosage forms and intermediate core parts thereof. The enteric coated dosage forms are administration to a subject.

Additionally, none of the cited references teach or describe combining a dry dosage form of proton pump inhibitor and a buffer with an aqueous diluent. Indeed, with the prior art teaching that non-enteric-coated forms are unstable to humidity (See Lovgren '505 patent, Col. 1-2), and that they must be enteric-coated, there was no expectation that such forms would be stable, let alone that they could be used to create liquid forms.

Therefore, the disclosures of the Oishi et al. patents do not anticipate pending claims 662-665, 753-756, 792-795, 827-831.

(x) Summary

The disclosures of Oishi *et al.,* Japanese Patent Application Nos. 05194224 (Oishi '224), and 05194225 (Oishi '225) do not anticipate the present claimed invention. For a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art. The prior art reference must also be enabling, placing the allegedly disclosed matter in the possession of the public. As discussed above, the emphasis of the cited references is on using buffering agents in an intermediate core part to prevent degradation of the proton pump inhibitor by the enteric coating—not gastric acid.

Oishi '225 and '224 also do not enable one of ordinary skill to practice the present claimed invention. As stated by the Federal Circuit: "[O]ur precedent states that a reference must be enabling to be prior art, that precedent simply means that a reference...is prior art only for that which the reference enables." Thus, an anticipatory reference must be enabling, that is, it

must put the claimed invention in the hand of one skilled in the art. Both Oishi '225 and '224 fail these tests.

Additionally, the Oishi references contain no disclosure regarding the use of flavoring or anti-foaming agents in any of the claimed dosage forms.

Therefore, the Oishi *et al* patents do not anticipate Applicant's claims. Reconsideration and withdrawal of this rejection is respectfully requested.

III. Rejections Under 35 U.S.C. § 103

Claims 23-180, 300-398, 461-559 were rejected under 35 U.S.C. § 103(a) as being unpatentable over JP05194224 or JP05194225 by Oishi *et al.* optionally in view of U.S. Patent No. 5,447,918 by McCullough or U.S. Patent No. 5,792,473 by Gergely *et al.* The Examiner stated that the two primary references teach anti-ulcer compositions containing benzimidazoles with buffer. The secondary references teach that adding antifoaming agent and/or flavoring agent in a pharmaceutical composition are conventional rendering the claims unpatentable Claims 300-398, 461-559 have been canceled, and independent claims 23, 95, and 141, have been amended to better define the invention.

This rejection is respectfully traversed. The burden of establishing a *prima facie* case of obviousness lies with the Examiner. In determining obviousness, one must focus on the invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 USPQ 2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is: "Whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success.... Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure." *In re Dow Chemical*, 5 USPQ 2d 1531 (Fed. Cir.

1988). When all the prior art is considered together, a person having ordinary skill in the art must have a sufficient basis for the necessary predictability of success to sustain a rejection under 35 U..S.C § 103. See Ex parte Novitski 26 USPQ2d 1389 (Bd.Pat.App. & Int. 1993) Citing In re Clinton, 188 USPQ 365 (CCPA 1976).

(i) Claims 23, 26-35, 38-40, 42, 43, 52, 53, 65-70, 81-86, and 91-94

As the claims now stand in front of the Patent Office, claim 23 claims a solid composition in a dosage form that is **not enteric-coated**, consisting essentially of a proton pump inhibitor, and at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. The dosage form is in the form of a suspension tablet, a chewable tablet, an effervescent powder, and an effervescent tablet. Claims 26-35, 38-40, 42, 43, 52, 53, 65-70, 81-86, 91-94 depend from claim 23.

The disclosures of the cited references do not render the pending claims obvious. The emphasis of the two primary references, the Oishi *et al.* patents, is on using buffering agents in an intermediate core part to prevent acid degradation of the proton pump inhibitor by the enteric coating. The secondary references teach adding antifoaming agent and/or flavoring agent to a pharmaceutical composition. JP05255088 teaches an enteric preparation produced by coating a core part containing benzimidazole compound with 1-2 layers of undercoating, and then applying an enteric coating agent thereupon. JP05255088, at abstract. JP05294831 teaches a preparation composed of a core part containing omeprazole and an alkaline compound and one

or more intermediate layers formed on the core part and an enteric coating film formed thereon. JP05294831, abstract.

The cited references also teach away from Applicant's claimed invention by emphasizing that suitable dosage forms must employ buffering agents **and** enteric coatings. For example, JP052924831 states that:

"[I]t is clear that oral dosage forms of omeprazole must be protected from contact with acidic reactive juices so that it can reach the small intestine without being degraded." JP052924831 at passage [003]. JP052924831 then teaches that the way to go about protecting the omeprazole from degradation is by enteric coating the omeprazole: "In order to obtain a dosage form preparation that prevents contact between omeprazole and acidic gastric juices, **the core part must be coated with an enteric coating.**" JP052924831, at [005] (emphasis added). Similarly, JP05255088 also teaches enteric preparations. There is thus a teaching away from the interaction in the stomach of a proton pump inhibitor and the low pH gastric secretions. Such teaching away rebuts obviousness. See In re Sponnoble, 405 F.2d 578, 587 (CCPA 1969); In re Caldwell, 319 F.2d 254, 256 (CCPA 1963).

Furthermore, until the present invention, those skilled in the art thought that the administration of an acid labile proton pump inhibitor without an enteric coating to be unworkable. Applicant recognized the problems associated with the delayed release dosage forms (e.g., lack of liquid forms, difficulty in swallowing by children, elderly and critically ill, slow onset of action, difficulty of manufacture, etc.) and solved them by the present invention. Consequently, Applicant's claims to dosage forms, compositions and methods employing non-enteric-coated proton pump inhibitor are not obvious.

Because of such a lack of expectation of success for dosage forms released in the stomach, the use of flavoring agents and anti-foaming agents such as simethicone are also non-obvious. According to the Federal Circuit in In re Oetiker, 977 F.2d 1443, 1447 (Fed. Cir. 1992, "[t]here must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination." Here, as shown above, the prior art tells the skilled artisan that proton pump inhibitors must be enteric-coated and, therefore, there was no reason or suggestion to use flavoring agents or anti-foaming agents because such agents would serve no purpose with the enteric-coated forms of the prior art. Thus, the cited references fail to render Applicant's claims obvious.

The Oishi *et al.* patents, Japanese Patent Application Nos. 05194224 and 05194225, focus on preparing enteric coated dosage forms and intermediate core parts thereof. Specifically, Oishi '225 teaches a "preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, with a benzimidazole compound that has antiulcer action and is not stable in acids." Oishi '225, at claim 1. Oishi '225 states that this preparation can be a "tablet, granule or capsule" Oishi '225, at claim 5; [0004]. However, when read in context of the entire specification, such tablets, granules and capsules refer to intermediate forms that are then enteric coated for the finished dosage forms. Oishi '225, at [0001].

Additionally, the cited references simply do not teach or suggest the present claimed invention. Section [0004] on page 5 of Oishi '225 describes how the intermediate core compositions are obtained by uniformly blending the benzimidazole compound, the amino acid, amino acid acid salt or amino acid alkali salt stabilizer, the buffering agent, additives, and water. Amounts of these substances disclosed are in the ranges of 0.01-10 parts by weight of amino acid

and 0.01-10 parts by weight of buffer with respect to 1 part by weight of benzimidazole compound.

However, none of the embodiments in Oishi '225 teach or suggest the present claimed invention where the composition has a buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. As illustrated above in Table No. 1, the amount of buffering agent in the embodiments of Oishi '225 is **never greater than 2.5 mg.**

Oishi '225 states further that the "resulting mixture is then finely granulated with a wet granulator, and the material is then subjected to tabletization to produce uncoated tablets for tablet production. Alternatively, the material can be granulated using an extrusion granulator, and then formed into core granules for producing granules." Oishi '225, at [0004] (emphasis added). The application then states that "[t]he uncoated or core granules **obtained in this manner** can be formed into an enteric preparation by coating the core granules with enteric coating," and that:

> The **enteric tablet or granule** that is of a dosage form that is **appropriate for oral administration** can be obtained as described above, and in addition, the granules can be packaged into capsules to produce a capsule. The **preparation obtained in this manner** experiences little change in external appearance even over long-term storage, and exhibits excellent stability with almost no decrease in content. As a result, the preparations can be used in the treatment of digestive ulcers in mammals including humans.

Oishi '225 at [0005].

There is thus no suggestion or teaching in Oishi '225 that the intermediate tablets and granules are suitable for oral administration. Indeed, it is only the enteric "preparation obtained in this manner" from the passage above at [0005] of ''225 that is appropriate for oral

administration and can be used to treat digestive ulcers. Therefore, it does not render Applicant's claims obvious.

Oishi '224 teaches when benzimidazole compounds that are unstable in acid are compounded with a combination of aluminum glycinate and buffering agent, the benzimidazole compounds is markedly stabilized, and coloration does not take place. Oishi '224, at abstract. Oishi '224 further teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added). The problem solved by Oishi '224 is that it is necessary to stabilize the compounds before making compounds into preparations for oral administration. Oishi '224 discovered that the preparations can be stabilized during the preparation of oral dosage forms through the use of aluminum glycinate and buffering agent. Oishi '224 at [0002]. Amounts of the buffering agent disclosed range from 0.01-20 parts by weight with respect to 1 part by weight of the benzimidazole compound. Oishi '224 at [0003].

However, none of the embodiments in Oishi '224 teach or suggest the present claimed invention where the composition has at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. As illustrated in Table No. 2, above, the amount of buffering agent in the embodiments of Oishi '224 is **never greater than 2.0 mg**. Therefore, it does not render Applicant's claims obvious.

Further, secondary considerations such as unexpected results and fulfilling an unmet need, etc., are indicia of unobviousness of the present claimed invention. As stated above, until the present invention, those skilled in the art believed that the administration of an acid labile

proton pump inhibitor without an enteric coating to be unworkable. In this regard, the cited references emphasize that suitable dosage forms must employ buffering agents **and** enteric coatings. There is thus a teaching away from the interaction in the stomach of a proton pump inhibitor and the low pH gastric secretions. Such teaching away rebuts obviousness. Furthermore, prior to the present invention the Applicant recognized that there was a need to provide additional dosage forms other than the delayed release dosage forms. Problems associated with difficulty in swallowing of these delay released dosage form by children, the elderly and critically ill patients were recognized by the Applicant. Additionally, other problems such as the slow onset of enteric coated dosage forms, the difficulty in manufacturing, etc., are solved by the present invention.

In this regard, the Applicant set out to solve the problems associated with the enteric coated dosage forms. For example, in Example VI on page 66 of the specification, the Applicant performed a study where patients with two or more risk factors for stress-related mucosal damage and a gastric pH of less than or equal to 4.0 prior to treatment were administered a solution of 2mg/ml omeprazole/1 ml 8.4% $NaHCO_3$. The patients received an initial dose of 40 mg of omeprazole solution followed eight hours later by another 40 mg dose, then 20 mg of omeprazole was administered per day for five days.

Two hours after the initial 40 mg dose of buffered omeprazole solution, all patients had an increase in gastric pH of greater than 8.0, as shown in Figure 1. Ten of the eleven patients maintained a gastric pH of greater than or equal to four when administered 20 mg omeprazole solution. One patient having a closed head injury and a total of five risk factor for stress-related mucosal damage required 40 mg omeprazole solution. Two patients were changed to omeprazole solution after having developed clinically significant upper gastrointestinal bleeding

while receiving conventional intravenous H_2-antagonists. Bleeding subsided in both cases after twenty-four hours. This study demonstrates that the present claimed invention is efficacious in controlling gastric pH in patients with two or more risk factors for stress-related mucosal damage and a gastric pH of less than or equal to 4.0 prior to treatment.

The Applicant also studied the efficacy of buffered omeprazole solution in ventilated patients. See Example IX, pages 71-72. Seventy-five adult mechanically ventilated patients with at least one additional risk factor for stress-related mucosal damage received 20 ml of a 2mg omeprazole/1 ml 8.4% $NaHCO_3$ initially, followed by a second 20 ml dose six to eight hours later, then 10 ml daily. No patient experienced clinically significant upper gastrointestinal bleeding after receiving omeprazole suspension. The four-hour post omeprazole gastric mean pH was 7.1, the mean gastric pH after starting omeprazole was 6.8, and the lowest mean pH after starting omeprazole was 5.6. Thus, omeprazole solution prevented clinically significant upper gastrointestinal bleeding and maintained pH above 5.5 in mechanically ventilated critical care patients without producing toxicity. This study demonstrates that the present claimed invention is efficacious in controlling gastric pH in mechanically ventilated critical care patients at risk for stress-related mucosal damage.

In another study performed by the Applicant, adult males admitted to the surgical intensive care and burn unit of the University of Missouri Hospital were studied. The patients had a gastric pH of less than 4.0, two or more stress-related mucosal damage risk factors, and were mechanically ventilated. See Example IX, pages 73-74. Patients were initially administered a 40 mg dose of a 2mg omeprazole/1 ml 8.4% $NaHCO_3$ solution, followed by a second 40 mg dose six to eight hours later, then a 20 mg daily dose. Each dose was administered through a nasogastric tube.

Two patients were excluded from the efficacy evaluation because the protocol for omeprazole administration was not followed. In one case the omeprazole enteric-coated pellets had not completely broken down prior to administration of the first two doses, which produced an erratic effect on gastric pH. The gastric pH increased to above 6.0 as soon as the patient was given a dose of omeprazole in which the enteric coated pellets were allowed to completely breakdown.

The mean pre-omeprazole gastric pH was 3.5. Within four hours of omeprazole administration, the gastric pH rose to 7.1 The mean gastric pH during omeprazole administration was 6.8, and the lowest gastric pH was 5.6. No clinically significant upper gastrointestinal bleeding occurred during omeprazole therapy, and the gastric pH was maintained above 4.0 on omeprazole 20 mg/day in seventy-three of the seventy-five patients. This experiment demonstrates that the omeprazole solution is a safe and effective therapy for the prevention of clinically significant stress-related mucosal bleeding in critical care patients.

These examples clearly illustrate the efficacy of the buffered omeprazole solution of the present claimed invention based on the increase in gastric pH, safety, and costs of the buffered omeprazole solution for stress-related mucosal damage prophylaxis. These examples also show that the Applicant recognized several problems with dosing enteric coated delay release dosage forms and solved these problems. These efforts and results also clearly rebut the teachings of the cited references that those skilled in the art thought that the administration of an acid labile proton pump inhibitor without an enteric coating to be unworkable. The cited references emphasize that suitable dosage forms must employ buffering agents **and** enteric coatings.

The Examiner stated that McCullough teach that adding antifoaming agent and/or flavoring agent in a pharmaceutical composition are conventional rendering the claims unpatentable. However, McCullough does not teach or suggest the present claimed invention.

The disclosures of the cited references thus do not render the pending claims obvious. Reconsideration and withdrawal of this rejection is respectfully requested.

(ii) Claims 95-123, 127-140

As the claims now stand in front of the Patent Office, claim 95 claims a method of treating an acid-related gastrointestinal disorder by enterally administering to a subject a solid pharmaceutical composition in a dosage form that is **not enteric-coated**, wherein the composition consists essentially of a proton pump inhibitor, and at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in the subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. Claim 96-123, and 127-140 depend from claim 95.

Because there is no teaching or suggestion in the Oishi *et al.* patents as to the oral administration of the intermediate cores, Applicant's method claims are not rendered obvious by these references. Also, as discussed above, the cited references teach away from Applicant's claimed invention by emphasizing that suitable dosage forms must employ buffering agents **and** enteric coatings. For example, Oishi '224 teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added). Thus, these cited reference teach away

from the interaction in the stomach of a proton pump inhibitor and the low pH gastric secretions. Such teaching away rebuts obviousness.

Additionally, none of the embodiments in Oishi '225 teach or suggest the present claimed invention where the composition has a buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. As illustrated above in Table No. 1, the amount of buffering agent in the embodiments of Oishi '225 is **never greater than 2.5 mg.**

Furthermore, none of the embodiments in Oishi '224 teach or suggest the present claimed invention where the composition has at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. As illustrated in Table No. 2, above, the amount of buffering agent in the embodiments of Oishi '224 is **never greater than 2.0 mg**.

As mentioned above, the Oishi patents also teach away from Applicant's claimed invention by emphasizing that suitable dosage forms must employ buffering agents **and** enteric coatings. There is thus a teaching away from the interaction in the stomach of a proton pump inhibitor and the low pH gastric secretions. Such teaching away rebuts obviousness.

The disclosures of the cited references thus do not render the pending claims obvious. Reconsideration and withdrawal of this rejection is respectfully requested.

(iii) Claims 141, 144-163, 167-180

As the claims now stand in front of the Patent Office, claim 141 claims a composition, consisting essentially of a proton pump inhibitor; gastric secretions; and at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by the gastric secretions so as to achieve bioavailability of the proton pump inhibitor in a subject; wherein the proton pump inhibitor and the buffering agent comprise a solid dosage form, which is capable of disintegration and dissolution in the gastric secretions and is **not enteric-coated.** Claims 142, 144-163, 167-180 are dependent from claim 141.

The Oishi *et al.* patents focus on preparing enteric coated dosage forms and intermediate core parts thereof. These references do not teach or suggest the present claimed composition of claims 141-142, 144-163, 167-180 that contain at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by the gastric secretions so as to achieve bioavailability of the proton pump inhibitor in a subject, and where the proton pump inhibitor and the buffering are in a solid dosage form that is capable of disintegration and dissolution in the gastric secretions and is **not enteric-coated.**

The Oishi *et al.* patents do not teach or suggest the oral administration of the uncoated intermediate cores, nor do the cores meet the limitations of the Claims. Consequently, there is no teaching or suggestion that such intermediate cores interact with gastric secretions to form the composition as claimed by Applicant. Indeed, the prior art teaches that such cores must have enteric coatings to protect the proton pump inhibitor from the gastric secretions. There is thus no teaching or suggestion in Oishi '225 or in Oishi '224 that the intermediate tablets and granules are suitable for oral administration. Indeed, it is only the enteric "preparation obtained in this manner" from these references that is appropriate for oral administration and can be used to treat digestive ulcers.

Also as discussed above, the cited references teach away from Applicant's claimed invention by emphasizing that suitable dosage forms must employ buffering agents **and** enteric coatings. For example, Oishi '224 teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added). Thus, these cited reference teach away from the interaction in the stomach of a proton pump inhibitor and the low pH gastric secretions. Such teaching away rebuts obviousness.

Additionally, none of the embodiments in Oishi '225 teach or suggest the present claimed invention where the composition has a buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. As illustrated above in Table No. 1, the amount of buffering agent in the embodiments of Oishi '225 is **never greater than 2.5 mg.**

Furthermore, none of the embodiments in Oishi '224 teach or suggest the present claimed invention where the composition has at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. As illustrated in Table No. 2, above, the amount of buffering agent in the embodiments of Oishi '224 is **never greater than 2.0 mg.**

The disclosures of the cited references thus do not render the pending claims obvious. Reconsideration and withdrawal of this rejection is respectfully requested.

(iv) New Claims 622-654

As the claims now stand in front of the Patent Office, claim 622 claims a solid pharmaceutical composition in a dosage form that is **not enteric-coated.** The composition contains a **non-enteric coated** proton pump inhibitor, and a mixture of sodium bicarbonate and a calcium salt. The mixture of sodium bicarbonate and calcium salt is in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. Claims 623-645 depend from claim 622.

As mentioned above, the Oishi *et al.* patents focus on preparing enteric coated dosage forms and intermediate core parts thereof. These references do not teach or suggest the present claimed composition of claims 622-645 that is in a dosage form that is **not enteric coated,** and contains a mixture of sodium bicarbonate and calcium salt in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form.

Oishi '225 does not describe or teach the present claimed invention where the composition has a mixture of sodium bicarbonate and a calcium salt in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form. As illustrated above in Table No. 1, the amount of buffering agent in the embodiments of Oishi '225 is **never greater than 2.5 mg.**

Similarly, Oishi '224 teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi

'224, at [0001] (emphasis added). As illustrated above in Table No. 2, the amount of buffering agent in the embodiments of Oishi '224 is **never greater than 2.0 mg**.

Additionally, the combination of sodium bicarbonate and calcium carbonate is not obvious because it is not suggested by the prior art, and it provides enhanced treatment options as compared to either agent alone in certain circumstances for the following reasons:

1. Calcium carbonate (and other calcium salts) is a parietal cell activator, which can improve the efficacy of the proton pump inhibitor PPI. *See* page 42 of the Specification.

2. The use of calcium carbonate is advantageous in maintaining buffering capacity without increasing the sodium load from sodium bicarbonate, which is important in certain patients, such as those with hypertension or congestive heart failure.

3. The use of calcium carbonate is advantageous in providing additional dietary calcium, which is helpful in preventing and treating osteoporosis.

4. The use of calcium carbonate is advantageous in that it has better a flavor than sodium bicarbonate, and causes less gastric reflux and belching.

Also as discussed above, the Oishi patents teach away from Applicant's claimed invention by emphasizing that suitable dosage forms must employ buffering agents **and** enteric coatings. For example, Oishi '224 teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added). Thus, these cited reference teach away from the interaction in the stomach of a proton pump inhibitor and the low pH gastric secretions. Such teaching away rebuts obviousness.

Therefore, the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 by McCullough or U.S. Patent No. 5,792,473 by Gergely *et al.* do not render claims 622-654 obvious.

(v) New Claims 666-717

As the claims now stand in front of the Patent Office, claim 666 claims a solid pharmaceutical composition in a dosage form that is not enteric-coated. The composition consists essentially of a non-enteric coated proton pump inhibitor, and a buffering agent in an amount more than about 20 times the amount of the proton pump inhibitor on a weight to weight basis in the composition. Claims 667-717 depend from claim 666.

The Oishi *et al.* patents focus on preparing enteric coated dosage forms and intermediate core parts thereof. Applicant's claims to non-enteric dosage forms are not obvious in light of the cited references because there is no teaching of a non-enteric coated proton pump inhibitor and a buffering agent that is in an amount more than about 20 times the amount of the proton pump inhibitor on a weight to weight basis in the composition. These references also do not teach or suggest the present claimed compositions that contain at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by the gastric secretions so as to achieve bioavailability of the proton pump inhibitor in a subject.

Also as discussed above, the cited references teach away from Applicant's claimed invention by emphasizing that suitable dosage forms must employ buffering agents **and** enteric coatings. For example, Oishi '224 teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added). Thus, these cited reference teach away

from the interaction in the stomach of a proton pump inhibitor and the low pH gastric secretions. Such teaching away rebuts obviousness.

Additionally, the amount of buffering agent claimed by Applicant is critically distinct from the amounts of buffering agent taught by the Oishi *et al.* patents for intermediate core parts. As detailed in the attached Declaration of Joseph B. Schwartz Under 37 C.F.R. §1.132, incorporated herein by reference, when more than 20 parts of buffering agent is used in proportion to 1 part proton pump inhibitor, the protection against gastric acid degradation is significantly better than when less than 20 parts of buffering agent is employed.

Therefore, the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 by McCullough or U.S. Patent No. 5,792,473 by Gergely *et al.* do not render claims 666-717 obvious.

(vi) Method Claims: 203-222, 226-237; and New Method Claims: 655-661, 718-724, 725-728, 747-752, and 785-791

As the claims now stands in front of the Patent Office, Claims 203 a method of treating an acid-related gastrointestinal condition in a subject in need thereof, by enterally administering to the subject the solid pharmaceutical dosage form as recited in Claim 181. Claims 204-222, 226-237 are depend from claim 203. Claim 655 claims a method for treating an acid-related gastrointestinal disorder in a subject in need thereof, comprising: enterally administering to the subject the solid pharmaceutical composition as recited in Claim 622. Claims 656-661 are depend from claim 655. Claim 718 claims a method for treating an acid-related gastrointestinal disorder in a subject in need thereof, comprising: enterally administering to the subject the solid pharmaceutical composition as recited in Claim 666. Claims 719-724 are depend from claim

718. Claim 725 claims a method for administering a liquid pharmaceutical composition to a subject, by combining the pharmaceutical composition as recited in Claim 666 with an aqueous medium to form a suspension, and orally administering the suspension to the subject in a single dose without administering an additional buffering agent. Claims 726-728 are depend from claim 725. Claim 747 claims a method for treating an acid-related gastrointestinal disorder in a subject in need thereof, comprising: enterally administering to the subject the solid pharmaceutical composition as recited in Claim 23. Claims 748-752 depend from claim 841. Claim 785 claims a method for treating an acid-related gastrointestinal disorder in a subject in need thereof, comprising: enterally administering to the subject the solid pharmaceutical composition as recited in Claim 141. Claims 786-791 depend from claim 785.

Because there is no teaching or suggestion in the Oishi *et al.* patents as to the oral administration of the intermediate cores, Applicant's method claims are not obvious in light of these patents. As mentioned above, the Oishi *et al.* patents focus on preparing enteric coated dosage forms and intermediate core parts thereof. The enteric coated dosage forms are administration to a subject.

Specifically, Oishi '225 teaches a "preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, with a benzimidazole compound that has antiulcer action and is not stable in acids." Oishi '225, at claim 1. Oishi '225 states that this preparation can be a "tablet, granule or capsule" Oishi '225, at claim 5; [0004]. However, when read in context of the entire specification, such tablets, granules and capsules refer to intermediate forms that are then enteric coated for the finished dosage forms. This is emphasized by Oishi '225's description of the prior art and problems to be solved by the invention:

> With preparations such as tablets, fine powders, granules, capsules and dispersions, the compounds are influenced by other components of the preparation formula and become unstable, leading to a decrease in content and discoloration over time. Among these preparations, **when the compounds are coated to produce granules, they have poor compounding properties with respect to enteric bases** (cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, and methacrylic acid acrylic acid copolymer), and suffer content decrease and discoloration. **When an oral preparation is to be manufactured** in this manner using benzimidazole compound, in addition to problems arising from the **need for compounding with other components and the use of enteric base coatings**, there are also difficulties with formulation due to the detrimental influences on stability as described above. Consequently, it is **necessary** to appropriately stabilize these compounds when they are to be formulated in oral dosage forms.

Oishi '225, at [0001] (emphasis added).

Similarly, Oishi '224 teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added).

Therefore, the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 by McCullough or U.S. Patent No. 5,792,473 by Gergely *et al.* do not render claims 203-222, 226-237, 655-661, 718-724, 725-728, 747-752, and 785-791 obvious.

Reconsideration and withdrawal of this rejection for claims 203-222 and 226-237 is respectfully requested.

(vii) New Liquid Claims: 662-665, 753-756, 792-795, 827-831

As the claims now stand in front of the Patent Office, claim 662 claims a liquid pharmaceutical composition, comprising: the dosage form as recited in Claim 622 suspended in an aqueous medium. Claims 663-665 depend from claim 662. Claim 753 claims a liquid

pharmaceutical composition, comprising the pharmaceutical composition as recited in Claim 23 and an aqueous medium. Claims 754-756 depend from claim 753. Claim 792 claims a liquid pharmaceutical composition, comprising the pharmaceutical composition as recited in Claim 141 and an aqueous medium. Claims 793-795 depend from claim 792. Claim 827 claims a liquid pharmaceutical composition, comprising the pharmaceutical composition as recited in Claim 181 and an aqueous medium. Claims 828-831 depend from claim 827.

Because there is no teaching or suggestion in the Oishi *et al.* patents as to liquid pharmaceutical compositions, Applicant's method claims are not obvious in light of these references. As mentioned above, the Oishi *et al.* patents focus on preparing enteric coated dosage forms and intermediate core parts thereof. The enteric coated dosage forms are administration to a subject.

Also as discussed above, the cited references teach away from Applicant's claimed invention by emphasizing that suitable dosage forms must employ buffering agents **and** enteric coatings. For example, Oishi '224 teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added). Thus, these cited reference teach away from the interaction in the stomach of a proton pump inhibitor and the low pH gastric secretions. Such teaching away rebuts obviousness.

None of the cited references teach or suggest combining a dry dosage form of proton pump inhibitor and a buffer with an aqueous diluent. Indeed, with the prior art teaching that non-enteric-coated forms are unstable to humidity (See Lovgren '505 patent, Col. 1-2), and that they must be enteric-coated, there was no expectation that such forms would be stable, let alone that they could be used to create liquid forms.

Therefore, the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 by McCullough or U.S. Patent No. 5,792,473 by Gergely *et al.* do not render claims 662-665, 753-756, 792-795, 827-831 obvious.

(viii) Summary

The disclosures of Oishi *et al.,* Japanese Patent Application Nos. 05194224, and 05194225, optionally in view of U.S. Patent No. 5,447,918 or U.S. Patent No. 5,792,473, do not render the present claimed invention obvious. In determining obviousness, one must focus on the invention as a whole. The primary inquiry is: "Whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success.... Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure." When all the prior art is considered together, a person having ordinary skill in the art must have a sufficient basis for the necessary predictability of success to sustain a rejection under 35 U.S.C. § 103. As discussed above, the emphasis of the primary references is on using buffering agents in an intermediate core part to prevent degradation of the proton pump inhibitor by the enteric coating—not gastric acid. The pending claims of the present invention are free of enteric coatings and therefore are not shielded from interacting with gastric acid secretions, and are specifically designed for disintegration and dissolution in the stomach whereas the enteric forms disintegrate and dissolve in the duodenum.

The Examiner also stated that McCullough teaches that adding antifoaming agent and/or flavoring agent in a pharmaceutical composition are conventional rendering the claims unpatentable. However, McCullough does not teach or suggest the present claimed invention.

Furthermore, the Oishi patents teach away from Applicant's claimed invention by emphasizing that suitable dosage forms must employ buffering agents **and** enteric coatings. Such teaching away rebuts obviousness. The 35 U.S.C. § 103 rejection is therefore improper. Reconsideration and withdrawal of this rejection is respectfully requested.

IV. Rejections Under 35 U.S.C. § 103

Claims 181-299, 399-460, and 500-621 were rejected under 35 U.S.C. § 103(a) as being unpatentable over JP05194224 or JP05194225 by Oishi *et al.* optionally in view of U.S. Patent No. 5,447,918 by McCullough or U.S. Patent No. 5,792,473 by Gergely *et al.* in combination with JP05255088 or JP05294831. The Examiner stated that the two primary references teach anti-ulcer composition containing benzimidazoles with buffer. The secondary references teach that adding antifoaming agent and/or flavoring agent and/or coated with one or more layers formed on the core part in a pharmaceutical composition are conventional rendering the claims unpatentable.

Claims 238-299, 399-460, and 500-621 have been canceled. Independent claims 181, and 203 have been amended to better define the invention.

This rejection is respectfully traversed. The burden of establishing a *prima facie* case of obviousness lies with the Examiner. In determining obviousness, one must focus on the invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 USPQ 2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is: "Whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success.... Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure." *In re Dow Chemical*, 5 USPQ 2d 1531 (Fed. Cir.

1988). When all the prior art is considered together, a person having ordinary skill in the art must have a sufficient basis for the necessary predictability of success to sustain a rejection under 35 U..S.C § 103. See Ex parte Novitski 26 USPQ2d 1389 (Bd.Pat.App. & Int. 1993) Citing In re Clinton, 188 USPQ 365 (CCPA 1976).

(i) Claims 181-202

As the claims now stand in front of the Patent Office, claim 181 claims a solid pharmaceutical composition in a dosage form that is **not enteric-coated.** The composition comprises **a first part** comprising a proton pump inhibitor, and **a second part surrounding the first part.** The second part comprises at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor in the subject after enteral administration of the dosage form.

Applicant's claims to two-part dosage forms are not rendered obvious by the cited references because there is no teaching or suggestion to use buffering agents to surround the proton pump inhibitor in a non-enteric coated dosage form. These references do not teach or suggest the present claimed compositions that is **not enteric coated** and contains at least one buffering agent in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor by the gastric secretions so as to achieve bioavailability of the proton pump inhibitor in a subject.

Reconsideration and withdrawal of this rejection is respectfully requested.

(ii) Claims 203-237

As the claims now stand in front of the Patent Office, claim 203 claims a method of treating an acid-related gastrointestinal condition in a subject in need thereof, comprising enterally administering to the subject the solid pharmaceutical dosage form as recited in Claim 181.

Because there is no teaching or suggestion in the Oishi *et al.* patents as to the oral administration of the intermediate cores, Applicant's method claims are not obvious in light of the cited references. As mentioned above, the Oishi *et al.* patents focus on preparing enteric coated dosage forms and intermediate core parts thereof. The enteric coated dosage forms are administration to a subject.

Specifically, Oishi '225 teaches a "preparation containing stabilized antiulcer agent, formed by blending amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, with a benzimidazole compound that has antiulcer action and is not stable in acids." Oishi '225, at claim 1. Oishi '225 states that this preparation can be a "tablet, granule or capsule" Oishi '225, at claim 5; [0004]. However, when read in context of the entire specification, such tablets, granules and capsules refer to intermediate forms that are then enteric coated for the finished dosage forms. This is emphasized by Oishi '225's description of the prior art and problems to be solved by the invention:

> With preparations such as tablets, fine powders, granules, capsules and dispersions, the compounds are influenced by other components of the preparation formula and become unstable, leading to a decrease in content and discoloration over time. Among these preparations, **when the compounds are coated to produce granules, they have poor compounding properties with respect to enteric bases** (cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, and methacrylic acid acrylic acid copolymer), and suffer content decrease and discoloration. **When an oral preparation is to be manufactured**

> in this manner using benzimidazole compound, in addition to problems arising from the **need for compounding with other components and the use of enteric base coatings**, there are also difficulties with formulation due to the detrimental influences on stability as described above. Consequently, it is **necessary** to appropriately stabilize these compounds when they are to be formulated in oral dosage forms.

Oishi '225, at [0001] (emphasis added).

Similarly, Oishi '224 teaches that "production of **oral** preparations of benzimidazole compounds requires compounding with other ingredients and **an enteric coating**...." Oishi '224, at [0001] (emphasis added).

Reconsideration and withdrawal of this rejection is respectfully requested.

(iii) New Claims 622-654

Claims 622-645 are not obvious in light of the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 or U.S. Patent No. 5,792,473 in combination with JP05255088 or JP05294831, because, as stated above, the Oishi *et al.* patents do not teach or suggest the present claimed invention, and they teach away from the present claimed invention.

Therefore, the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 by McCullough or U.S. Patent No. 5,792,473 by Gergely *et al.* in combination with JP05255088 or JP05294831 do not render claims 622-654 obvious.

(iv) New Claims 666-717

Claims 666-717 Claims 622-645 are not obvious in light of the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 or U.S. Patent No. 5,792,473 in combination with JP05255088 or JP05294831, because, as stated above, the Oishi *et al.* patents do not teach

or suggest the present claimed invention, and they teach away from the present claimed invention. Reconsideration and withdrawal of this rejection is respectfully requested.

Therefore, the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 by McCullough or U.S. Patent No. 5,792,473 by Gergely *et al.* in combination with JP05255088 or JP05294831 do not render claims 666-717 obvious.

(v) Method Claims: 203-222, 226-237; and New Method Claims 655-661, 718-724, 725-728, 747-752, and 785-791

Claims 203-222, 226-237, 655-661, 718-724, 725-728, 747-752, and 785-791 are not obvious in light of the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 or U.S. Patent No. 5,792,473 in combination with JP05255088 or JP05294831, because, as stated above, the Oishi *et al.* patents do not teach or suggest the present claimed invention, and they teach away from the present claimed invention.

Therefore, the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 by McCullough or U.S. Patent No. 5,792,473 by Gergely *et al.* in combination with JP05255088 or JP05294831 do not render claims 203-222, 226-237, or new claims 655-661, 718-724, 725-728, 747-752, and 785-791 obvious.

Reconsideration and withdrawal of this rejection is respectfully requested for claims 203-222 and 226-237.

(vi) New Liquid Claims: 662-665, 753-756, 792-795, 827-831

Claims 662-665, 753-756, 792-795, and 827-831 are not obvious in light of the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 or U.S. Patent No. 5,792,473 in

combination with JP05255088 or JP05294831, because, as stated above, the Oishi *et al.* patents do not teach or suggest the present claimed invention. Also, these Oishi *et al.* patents teach away from the present claimed invention.

Therefore, the Oishi *et al.* patents optionally in view of U.S. Patent No. 5,447,918 by McCullough or U.S. Patent No. 5,792,473 by Gergely *et al.* in combination with JP05255088 or JP05294831 do not render claims 662-665, 753-756, 792-795, 827-831 obvious.

(viii) Summary

The disclosures of Oishi *et al.*, Japanese Patent Application Nos. 05194224, and 05194225, optionally in view of U.S. Patent No. 5,447,918 or U.S. Patent No. 5,792,473, do not render the present claimed invention obvious. In determining obviousness, one must focus on the invention as a whole. The primary inquiry is: "Whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success.... Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure." When all the prior art is considered together, a person having ordinary skill in the art must have a sufficient basis for the necessary predictability of success to sustain a rejection under 35 U..S.C. § 103. As discussed above, the emphasis of the cited references is on using buffering agents in an intermediate core part to prevent degradation of the proton pump inhibitor by the enteric coating—not gastric acid. The pending claims of the present invention are free of enteric coatings and therefore are not shielded from interacting with gastric acid secretions, and are specifically designed for disintegration and dissolution in the stomach whereas the enteric forms disintegrate and dissolve in the duodenum.

The Examiner also stated that McCullough teaches that adding antifoaming agent and/or flavoring agent in a pharmaceutical composition are conventional rendering the claims unpatentable. However, McCullough does not teach or suggest the present claimed invention.

Furthermore, the Oishi patents teach away from Applicant's claimed invention by emphasizing that suitable dosage forms must employ buffering agents **and** enteric coatings. Such teaching away rebuts obviousness. The 35 U.S.C. § 103 rejection is therefore improper. Reconsideration and withdrawal of this rejection is respectfully requested.

V. Conclusion

With entry of the above Amendment and in view of the foregoing remarks, it is respectfully requested that pending claims 23, 26-35, 38-40, 42, 43, 52, 53, 65-76, 81-86, 91-123, 127-141, 144-163, 167-181, 184-222, 226-237, and 622-861 are in condition for allowance. It is respectfully requested in view of the foregoing Amendment and Remarks that all of the objections and rejections in the Office Action dated August 31, 2001 have been overcome and should be withdrawn. Accordingly, reconsideration and withdrawal of the outstanding rejections and allowance of pending claims 23, 26-35, 38-40, 42, 43, 52, 53, 65-76, 81-86, 91-123, 127-141, 144-163, 167-181, 184-222, 226-237, and 622-861 is respectfully solicited. Applicant respectfully requests early and favorable notification to that effect. The Examiner is encouraged to contact the undersigned with any questions or to otherwise expedite prosecution.

Respectfully requested,

THE CURATORS OF THE
UNIVERSITY OF MISSOURI

By: MAYER, BROWN & PLATT

By: _____
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Dated: November 19, 2001

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Version with Markings to Show Changes Made to the Claims

23. (Amended) A solid pharmaceutical composition in a dosage form that is not enteric-coated[or delayed-released], consisting essentially of [comprising]:

(a) a proton pump inhibitor (PPI) selected from the [a] group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole; and

(b) at least one buffering agent [present] in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor (PPI) [PPI] by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor (PPI) [PPI] in the [a] subject after enteral [oral] administration of the dosage form;

wherein the dosage form is selected from the group consisting of suspension tablet, chewable tablet, effervescent powder, and effervescent tablet.

26. (Amended) The composition [dosage form] as recited in Claim 23, wherein the proton pump inhibitor [PPI] comprises a substantially pure enantiomer, [a]racemic mixture, [a]derivative, [or a] free base, or salt thereof.

27. (Amended) The composition [dosage form] as recited in Claim 23, wherein the proton pump inhibitor [PPI] is omeprazole.

28. (Amended) The composition [dosage form] as recited in Claim 23, wherein the proton pump inhibitor [PPI] is lansoprazole.

29. (Amended) The composition [dosage form] as recited in Claim 23, wherein the proton pump inhibitor [PPI] is rabeprazole.

30. (Amended) The composition [dosage form] as recited in Claim 23, wherein the proton pump inhibitor [PPI] is esomeprazole.

31. (Amended) The composition [dosage form] as recited in Claim 23, wherein the proton pump inhibitor [PPI] is pantoprazole.

32. (Amended) The composition [dosage form] as recited in Claim 23, wherein the proton pump inhibitor [PPI] is pariprazole.

33. (Amended) The composition [dosage form] as recited in Claim 23, wherein the proton pump inhibitor [PPI] is leminoprazole.

34. (Amended) The composition [dosage form] as recited in Claim 23, further comprising at least one flavoring agent.

35. (Amended) The composition [dosage form] as recited in Claim 23, further comprising an anti-foaming agent.

38. (Amended) The composition [dosage form] as recited in Claim 23, wherein the dosage form is a suspension tablet.

39. (Amended) The composition [dosage form] as recited in Claim 23, wherein the dosage form is a chewable tablet.

40. (Amended) The composition [dosage form] as recited in Claim 39, further comprising aspartame.

42. (Amended) The composition [dosage form] as recited in Claim 23, wherein the dosage form is an effervescent powder.

43. (Amended) The composition [dosage form] as recited in Claim 23, wherein the dosage form is an effervescent tablet.

52. (Amended) The composition [dosage form] as recited in Claim 23, wherein the buffering agent is at least [comprises about 250 mg to] about 1680 mg sodium bicarbonate.

53. (Amended) The composition [dosage form] as recited in Claim 23, wherein the buffering agent is [comprises] about 1000 [840] mg to about 1680 mg sodium bicarbonate.

65. (Amended) A method of producing a liquid pharmaceutical composition, comprising: [produced by the method of] combining the composition [dosage form] recited in Claim 38 with an aqueous medium.

66. (Amended) The method [liquid pharmaceutical composition] of Claim 65, wherein the aqueous medium comprises sodium bicarbonate solution.

67. (Amended) The method [liquid pharmaceutical composition] of Claim 65, wherein the aqueous medium comprises gastric secretions.

68. (Amended) The method [liquid pharmaceutical composition] of Claim 65, wherein the aqueous medium comprises water.

69. (Amended) A method of producing a liquid pharmaceutical composition, comprising: [produced by the method of] combining the composition [dosage form] recited in Claim 39 with an aqueous medium.

70. (Amended) The method [liquid pharmaceutical composition] of Claim 69, wherein the aqueous medium comprises sodium bicarbonate solution.

71. (Amended) The method [liquid pharmaceutical composition] of Claim 69 wherein the aqueous medium comprises gastric secretions.

72. (Amended) The method [liquid pharmaceutical composition] of Claim 69 wherein the aqueous medium comprises water.

73. (Amended) A method of producing a liquid pharmaceutical composition [produced by the method of], comprising combining the composition [dosage form] recited in Claim 40 with an aqueous medium.

74. (Amended) The method [liquid pharmaceutical composition] of Claim 73 wherein the aqueous medium comprises sodium bicarbonate solution.

75. (Amended) The method [liquid pharmaceutical composition] of Claim 73 wherein the aqueous medium comprises gastric secretions.

76. (Amended) The method [liquid pharmaceutical composition] of Claim 73 wherein the aqueous medium comprises water.

81. (Amended) A method of producing a liquid pharmaceutical composition, comprising: [produced by the method of] combining the composition [dosage form] recited in Claim 42 with an aqueous medium.

82. (Amended) The method [liquid pharmaceutical composition] of Claim 81, wherein the aqueous medium comprises sodium bicarbonate solution.

83. (Amended) The method [liquid pharmaceutical composition] of Claim 81, wherein the aqueous medium comprises water.

84. (Amended) A method of producing a liquid pharmaceutical composition, comprising: [produced by the method of] combining the composition [dosage form] recited in Claim 43 with an aqueous medium.

85. (Amended) The method [liquid pharmaceutical composition] of Claim 84, wherein the aqueous medium comprises sodium bicarbonate solution.

86. (Amended) The method [liquid pharmaceutical composition] of Claim 84, wherein the aqueous medium comprises water.

91. (Amended) A method of producing a liquid pharmaceutical composition, comprising: [produced by the method of] combining the composition [dosage form] recited in Claim 45 with an aqueous medium.

92. (Amended) The method [liquid pharmaceutical composition] of Claim 91, wherein the aqueous medium comprises sodium bicarbonate solution.

93. (Amended) The method [liquid pharmaceutical composition] of Claim 91, wherein the aqueous medium comprises gastric secretions.

94. (Amended) The method [liquid pharmaceutical composition] of Claim 91, wherein the aqueous medium comprises water.

95. (Amended) A method of treating an acid-related gastrointestinal disorder in a subject in need thereof [condition], comprising: enterally [orally] administering to the [a] subject a solid pharmaceutical composition in a dosage form that is not enteric-coated[or delayed-released], wherein the composition consists essentially of: [comprising]:

(a) a proton pump inhibitor (PPI) selected from the [a] group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole; and

(b) at least one buffering agent [present] in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor (PPI) [PPI] by gastric acid in the subject so as to achieve bioavailability of the proton pump inhibitor (PPI) [PPI] in the subject after enteral [oral] administration of the dosage form;

111. (Amended) The method as recited in Claim 95, wherein the proton pump inhibitor [PPI] comprises a substantially pure enantiomer, [a] racemic mixture, [a] derivative, [or a] free base, or salt thereof.

112. (Amended) The method as recited in Claim 95, wherein the composition [dosage form] further comprises a flavoring agent.

113. (Amended) The method as recited in Claim 95, wherein the composition [dosage form] further comprises an anti-foaming agent.

122. (Amended) The method as recited in Claim 95, wherein the composition [dosage form] is a plurality of pellets.

123. (Amended) The method as recited in Claim 95, wherein the composition [dosage form] is a plurality of granules.

130. (Amended) The method as recited in Claim 95, wherein the buffering agent is at least [comprises about 250 mg to] about 1680 mg sodium bicarbonate.

131. (Amended) The method as recited in Claim 95, wherein the buffering agent is [comprises] about 1000 [840] mg to about 1680 mg sodium bicarbonate.

141. (Amended) A composition, consisting essentially of [comprising]:

(a) a therapeutically effective amount of a non-enteric coated proton pump inhibitor (PPI) selected from the [a] group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole;

(b) gastric secretions; and

(c) at least one buffering agent [present] in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor (PPI) [PPI] by the gastric secretions so as to achieve bioavailability of the proton pump inhibitor (PPI) [PPI] in a subject,

wherein the proton pump inhibitor (PPI) [PPI] and the buffering agent comprise a solid dosage form, which is capable of disintegration and dissolution in the gastric secretions and is not enteric-coated or delayed-released.

144. (Amended) The composition as recited in Claim 141, wherein the proton pump inhibitor [PPI] comprises a substantially pure enantiomer, [a] racemic mixture, [a] derivative, [or a] free base, or salt thereof.

170. (Amended) The composition as recited in Claim 141, wherein the buffering agent is at least [comprises about 250 mg to] about 1680 mg sodium bicarbonate.

171. (Amended) The composition as recited in Claim 141, wherein the buffering agent is [comprises] about 1000 [840] mg to about 1680 mg sodium bicarbonate.

181. (Amended) A solid pharmaceutical composition in a dosage form that is not enteric-coated[or delayed-released], comprising:

(a) a first part comprising a non-enteric coated proton pump inhibitor (PPI) selected from the [a] group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole; and

(b) a second part surrounding the first part, the second part comprising at least one buffering agent present in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor (PPI) [PPI] by gastric acid in a subject so as to achieve bioavailability of the proton pump inhibitor (PPI) [PPI] in the [a] subject after enteral [oral] administration of the dosage form.

184. (Amended) The dosage form as recited in Claim 181, wherein the proton pump inhibitor [PPI] comprises a substantially pure enantiomer, [a] racemic mixture, [a] derivative, [or a] free base, or salt thereof.

198. (Amended) The dosage form as recited in Claim 181, wherein the buffering agent is at least [about 250 mg to] about 1680 mg sodium bicarbonate.

203. (Amended) A method of treating an acid-related gastrointestinal condition in a subject in need thereof, comprising: enterally [orally] administering to the [a] subject the [a] solid pharmaceutical dosage form as recited in Claim 181. [that is not enteric-coated or delayed-released, comprising:

(a) a first part comprising a proton pump inhibitor (PPI) selected from the [a] group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole; and

(b) a second part surrounding the first part, the second part comprising at least one buffering agent present in an amount sufficient to prevent or inhibit acid degradation of the proton pump inhibitor (PPI) [PPI] by gastric acid so as to achieve bioavailability of the proton pump inhibitor (PPI) [PPI] in the subject after oral administration of the dosage form.]

219. (Amended) The method as recited in Claim 203, wherein the proton pump inhibitor [PPI] comprises a substantially pure enantiomer, [a] racemic mixture, [a] derivative, [or a] free base, or salt thereof.

229. (Amended) The method as recited in Claim 203, wherein the buffering agent is at least [comprises about 250 mg to] about 1680 mg sodium bicarbonate.

230. (Amended) The method as recited in Claim 203, wherein the buffering agent is [comprises] about 1000 [840] mg to about 1680 mg sodium bicarbonate.

233. (Amended) The method as recited in Claim 203 wherein the buffering agent comprises a combination of sodium bicarbonate and calcium carbonate [bicarbonate].